Natural History of Chronic Hepatitis B in European Countries

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Chronic hepatitis B leads in about 15-40% of patients to serious morbidity or mortality;[1] conversely, chronic hepatitis B infection is not associated with major pathology in 60-85% of cases. The study of the natural history may elucidate what are major risk factors for disease progression and who is in need of antiviral therapy; conversely, what combination of factors characterizes inactive, non-progressive infection not needing antiviral therapy.

HBeAg is a marker of high viral replication and associated with disease progression. HBeAg seroconversion is considered a key event in the evolution of chronic hepatitis B.

Seroconversion is followed by resolution of biochemical and histologic signs of inflammatory activity.[2,3] Following this finding, chronic hepatitis B has been one of two types, which differ by HBeAg status. Chronic HBeAg-negative hepatitis was the non-progressive type. The discovery of high viral replication in chronic HBeAg-negative hepatitis and its mechanism of an HBV DNA mutation preventing expression of HBeAg has blurred the simple concept of non-progressive HBeAg-negative chronic hepatitis B.

In fact, chronic HBV infection presents as one of four potentially successive phases. For its classification, serum aminotransferase ALT and quantitative HBVDNA in addition to HBeAg status are required. In the *immunotolerant phase*, serum HBeAg is detectable; serum HBV-DNA levels are high; and serum aminotransferases normal or minimally elevated. In the *immunoactive phase*, serum HBV-DNA levels decrease and flares of aminotransferases may be observed. Over a period of months to years, these events are followed by HBeAg-antiHBe seroconversion. The *immune control phase* follows HBeAg-antiHBe seroconversion. HBV replication persists but at very low levels. This phase is usually termed the “inactive carrier state.” In some patients, HBeAg seroconversion is accompanied by the selection of HBV variants that are unable to produce HBeAg. A proportion of these HBeAg-negative patients may subsequently develop viral and liver disease reactivation, enter the *immune escape phase,* and progress to HBeAg-negative chronic hepatitis B.

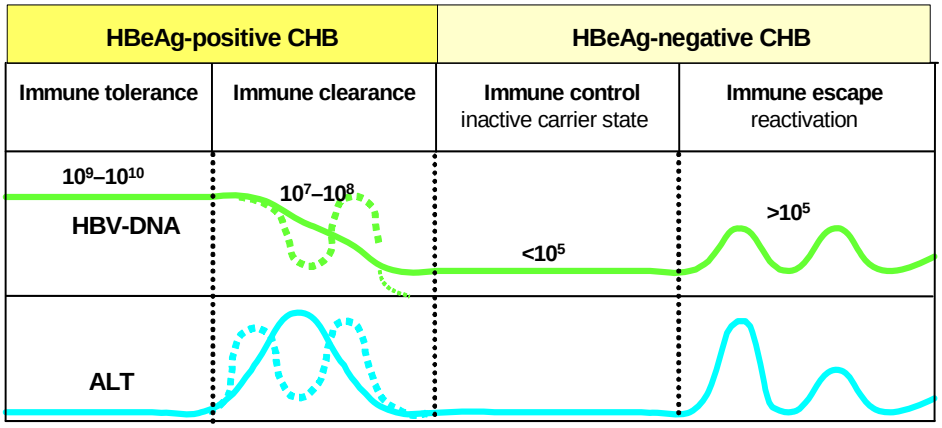

Fig: Classification of chronic hepatitis B in four phases based upon serum HBeAg status, complemented with quantitative HBVDNA reflecting the level of viremia, and serum ALT reflecting liver disease activity.

In two phases of chronic hepatitis B, the *immunoactive* and the *immune-escape/reactivation* phases, there usually is progressive liver disease, and antiviral therapy should be considered. In the *immune tolerance* phase and the *immune control/inactive carrier* phase, there are no signs of active liver disease (albeit the large difference in viremia) and no recommendation for antiviral therapy.

The statement on the benign course after HBeAg-seroconversion has recently been challenged for Asian patients infected at birth or early childhood.[4] However, two recent European studies have provided further evidence confirming the almost uniform non-progressive nature of the *immune control/inactive carrier state* phases.[5,6] The report from Bortolotti[5] describes 91 HBeAg-positive children who entered the long-term follow-up almost 30 years ago. Among 85 children without cirrhosis who seroconverted to anti-HBe, 80 became inactive carriers, 4 rapidly lost HBsAg, and 1 developed HBeAg-negative hepatitis. At the end of the follow-up, 68/80 were still inactive carriers, 9/80 had lost HBsAg, and 3/80 reactivated and developed HBeAg-negative hepatitis. In 4 children with cirrhosis and HBeAg seroclearance, 2/4 remained inactive carriers and 2/4 developed hepatocellular carcinoma. The second study comprised 296 blood donors found to be HBsAg-positive between 1972-1977.Their course was compared to 157 HBsAg-negative blood donors matched for age, sex, and alcohol intake. At entry to the study, all HBsAg carriers were HBeAg-negative, anti-HBe-positive, and all but four had normal ALT levels. After 22-32 years of follow-up 32/296 patients and 14/157 controls had died. Hepatocellular carcinoma caused death in 2/296 and 1/157 subjects (0.6% in each group); non-liver related death occurred in 29/296 of cases and in 13/157 controls. Survival was independently predicted by older age, abnormal gamma-glutamyl transpeptidase levels, and the presence of medical comorbidity at baseline. Fifty-nine (32%) carriers cleared HBsAg (yearly incidence: 1%).

The two studies point to the benign course of the inactive HBsAg-carrier state in European patients as well as to the key risk factors: cirrhosis, medical comorbidity, and alcohol abuse. Hepatitis B reactivation after HBeAg seroconversion is rare in European children compared to adult Asian patients referred to a liver clinic;[4] it was also hardly seen in European inactive HBsAg carriers identified at blood bank screening.

References

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